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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,435	10/21/2003	Mark F. Pittenger	640100.470	3718

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 09/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/690,435	PITTENGER ET AL.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-10 and 12-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 4-10 and 12-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response of June 26, 2006, to the non-final action dated January 12, 2006 has been entered. Claims 3 and 11 have been cancelled. Claims 1 and 4 have been amended. No claims were newly added. Claims 1-2, 4-10 and 12-21 are pending in the application and under current examination.

Election/Restriction

Upon further consideration, the restriction between Groups I and II, set forth in the office action dated November 3, 2005, is withdrawn and the claims rejoined.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2, 4-10 and 12-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4, 12 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: wherein said administered MSCs differentiate into cardiomyocytes in the heart of said individual, resulting in improved ventricular wall motion of the heart (claims 1 and 4); and wherein said administered MSCs differentiate into blood vessels in the heart of said individual, resulting in repairing or regenerating blood vessels, or promoting angiogenesis in the heart (claims 1 and 4).

Claims 1, 4, 12 and 17 are further unclear. The claims are drawn to methods of producing cardiomyocytes, improving ventricular wall motion, repairing blood vessels and stimulating or promoting angiogenesis in the heart of an individual, by administering (or administering intravenously, in claim 1), an effective amount of MSCs. It is not clear how the administration of MSCs by any route (or intravenously) would produce cardiomyocytes or promote angiogenesis

limited to the heart to an individual. The claims should recite: "administering to the heart of an individual", to be consistent with the preamble of the claims.

New Claim Rejections - 35 USC § 112-Scope of Enablement

Claims 12-21 are newly rejected under 35 U.S.C.§112, first paragraph, because the specification, while being enabling for a method producing cardiomyocytes and improving ventricular wall motion in a heart of an individual, comprising: administering to the heart of said individual a cardiomyocyte producing amount of autologous or allogeneic MSCs, wherein said administered MSCs differentiate into cardiomyocytes in the heart of said individual, resulting in improved ventricular wall motion of the heart, does not reasonably provide an enablement for a method of repairing or regenerating blood vessels, or a method of stimulating or promoting angiogenesis, as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection is based on two (2) separate issues: **1)** the absence of an enabling disclosure for the methods of repairing or regenerating blood vessels or stimulating or promoting angiogenesis in the heart of an individual by administering to said individual an effective amount of MSCs and **2)** the absence of an enabling disclosure for the aforementioned methods by administering said MSCs from any source, including xenogeneic, or MSCs that are genetically modified, as broadly claimed. In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404:

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the

invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

MPEP § 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection."

As a first issue **(1)**, the specification does not provide an enabling disclosure for the methods of repairing or regenerating blood vessels or stimulating or promoting angiogenesis in the heart of an individual by administering to said individual an effective amount of MSCs.

The specification states: "Applicants have discovered that the mesenchymal stem cells may stimulate and/or promote angiogenesis in the heart and/or repair or regenerate blood vessel of the heart" (pp. 9-10, bridging). While the engrafted MSCs were found to express numerous muscle specific proteins, and exhibited morphological changes consistent with myogenesis, the specification does not show the production of any vascular cell, or any evidence for the formation of arteries, veins and capillaries, formed as a result of administering MSCs to the heart. The specification discloses human and rat MSCs transplanted to athymic rats (Examples 1-3), and allogeneic MSCs transplanted by direct injection into infracted pig hearts (Examples 4 and 5, p. 15 and 18; and Fig. 3), resulting in improvements in wall motion scores over time (p. 17) as well as cystolic and diastolic wall thickness (p. 18). The specification discloses that the autologous MSCs were isolated from swine bone marrow, expanded in culture, and cryopreserved until the time of transplantation (p. 18). However, no additional information regarding said culture conditions or any additional alterations to the MSCs are provided. Moreover, while the specification discloses that MSCs were identified surrounding and associated with smooth muscle layer of blood vessels (Example 7, p. 20), it remains unknown whether the MSCs contributed to the formation of said blood vessels, as blood vessels were already present in the infracted pig heart.

The post-filing art of Lee et al. (Ann. Intern. Med. 140: 729-737; 2004) in reviewing the status of stem cell transplantation in myocardial infarction, notes that neovascularization is mediated by endothelial progenitor cells stimulated by GCSF (second column, p. 730). Further noting that autologous bone marrow cells secrete angiogenic factors, such as VEGF and macrophage chemoattractant protein 1, that stimulate the proliferation of endothelial cells (first

column, p. 731). The authors conclude that while preliminary data from animal models suggest that infracted myocardium may be regenerated by implanting stem cells, skepticism exists with this treatment method, especially given the initial excitement of angiogenesis studies that did not live up to expectations (second column, p. 735). Therefore, it remains unclear whether transplanted adult MSCs of the instant invention resulted in the repair and regeneration of blood vessels, as even the indirect contribution of the MSCs in providing angiogenesis promoting factors cannot be determined in an environment where such factors are continually supplied by various cells and tissues.

As a second issue **(2)**, the specification does not provide an enabling disclosure for the methods of repairing or regenerating blood vessels or stimulating or promoting angiogenesis in the heart of an individual by administering to said individual an effective amount of MSCs from any source, including xenogeneic, or MSCs that are genetically modified.

When given their broadest reasonable interpretation, in view of the as filed specification, claims 11-21 encompass methods of administering MSCs from any source, including cells that are xenogeneic in origin. The specification teaches that the MSCs may be genetically modified or engineered to contain genes which express proteins of importance for differentiation and/or maintenance of striated muscle cells (line 15-17, p. 4). The specification additionally envisions the use of MSCs "in accordance with the invention, in order of preference, autologous, allogeneic or xenogeneic (lines 15-16, p. 8). The specification fails to disclose adequate representations of MSCs that are genetically modified or engineered to contain genes which express proteins of importance for the differentiation and/or maintenance of striated muscle cells (as envisioned on p. 4, lines 15-18 of the instant specification); or the production of MSCs from a xenogeneic source (as stated in line 15, p. 8 of the instant specification). The specification discloses allogeneic MSCs used for transplantation in pig (Examples 4 and 5, pp. 15 and 18; and Fig. 3). The specification further describes the implantation of human MSCs into athymic rat myocardial tissue (Example 1, pp. 10-11). However, athymic rats lack the ability to mount an immune response against xenogeneic MSCs. Therefore, Example 1 does not represent a true xenogeneic transplant of MSCs to cardiac tissue.

The specification provides no additional examples of xenografts or transfer of genetically modified MSCs. The specification does not provide the guidance required to overcome the art-recognized unpredictability of transplant of genetically modified MSCs or xenografts.

The state of the prior art with regard to transplantation of MSCs and gene therapy are effectively summarized by the references of Prockop (Science 276:71-74, 1997; of record); Gerson, S. (Nature Medicine 5:262-264, 1999; of record); Saadi et al. (Life Sciences 62:365-387, 1998); and Verma et al. (Nature 389:239-242, 1997, of record).

The prior art at the time of filing suggests that MSC transplantation and *in vivo* therapeutic effectiveness have not been established such that utilizing these cells to treat diseases, disorders, or conditions is routine or predictable. For example, Prockop indicates that several different strategies are being pursued for therapeutic use of MSCs and notes that "Obviously, however, a number of fundamental questions about MSCs still need to be resolved before they can be used for safe and effective cell and gene therapy" (p. 74, center column). Similarly, Gerson indicates that many questions need to be addressed regarding the utilization of MSCs in therapeutic regimens (p. 264, left column). Thus, while the teachings indicate that mesenchymal or marrow stromal based therapies appear to be promising, the specific methodologies and clinical efficacy of such therapies remain to be established.

Additionally, transplantation of MSCs in the examples given utilizes autologous or allogeneic sources for the stem cells, as it is well recognized in the art that transplant of xenogeneic cells to a recipient induces a severe immune response, resulting in subsequent loss of transplanted tissue. Saadi et al. teach that success of xenotransplantation is confounded by tissue rejection caused by host immune responses. Various factors need to be considered for xenotransplantation, including selection of a donor species and the transplant's compatibility with the recipient, which could induce cellular or humoral rejection (Figure 1, p. 367). Furthermore, they conclude: "thus, it is not possible to predict that xenotransplantation will enter the clinical arena in a very few years (p. 381).

The guidance provided by the specification amounts to an invitation for the skilled Artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely discloses the production of cardiomyocytes by autologous or allogeneic MSCs following transfer of said MSCs to cardiac tissue.

The detail of the disclosure provided by Applicant, in view of the prior art, must encompass a wide knowledge, so that the Artisan of skill would be able to practice the invention as claimed by Applicant, without undue burden being imposed on such Artisan. This burden has not been met because it would require undue experimentation to MSCs from any source, including xenogeneic, or MSCs that are genetically modified, to repair or regenerate blood vessels or to stimulate or promote angiogenesis, as claimed in the instant application.

Therefore, in view of the art recognized high level of unpredictability where the transplantation of xenogeneic MSCs will likely produce a severe immune response and likely lead to tissue rejection, together with the large quantity of research required to define these unpredictable variables, and the lack of guidance provided in the specification regarding the contribution of MSCs to repair or regeneration of blood vessels, or promoting angiogenesis, it is the position of the examiner that it would require undue experimentation for one of skill in the art to practice the scope of the invention as broadly claimed. Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

Response to Obviousness Type Double Patenting

Claims 1-11 were previously rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,387,369, in the office action dated January 12, 2006. In view of the terminal disclaimer filed June 26, 2006, the previous rejection is withdrawn.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst William Phillips, whose telephone number is **(571) 272-0548**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is **(703) 272-**

3311. The examiner can normally be reached Monday through Friday, between 7:00-4:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on **(571) 272-0731**. The fax phone number for the organization where this application or proceeding is assigned is **(571) 273-8300**. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

For all other customer support, please call the USPTO Call Center (UCC) at **(800) 786-9199**.

Fereydoun G. Sajjadi, Ph.D.
Examiner, USPTO, AU 1633

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PRIMARY EXAMINER